(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 232 742 A1**

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 87100458.6

(22) Date of filing: 15.01.87

(51) Int. Cl.⁴: C07C 45/29 , C07C 49/00 , B01J 31/34

(30) Priority: 16.01.86 IT 1909886

(43) Date of publication of application: 19.08.87 Bulletin 87/34

(84) Designated Contracting States: BE CH DE FR GB LI NL

(71) Applicant: ISTITUTO GUIDO DONEGANI S.p.A.
Via Caduti del Lavoro
I-28100 Novara(IT)
Applicant: CONSIGLIO NAZIONALE DELLE RICERCHE
Piazzale Aldo Moro, 7
I-00198 Roma(IT)

(72) Inventor: Venturello, Carlo, Dr.
135, Via XXIII Marzo
I-28100 Novara(IT)
Inventor: Gambaro, Mario
5, Via Borrini
I-28067 Pernate Novara(IT)
Inventor: Ricci, Marco, Dr.
5, Via Brescia
I-28100 Novara(IT)

(74) Representative: Weinhold, Peter, Dr. et al
Patentanwälte Dr. V. Schmied-Kowarzik Dipl.-Ing. G. Dannenberg Dr. P. Weinhold Dr. D. Gudel Dipl.-Ing. S. Schubert Dr. P. Barz
Siegfriedstrasse 8
D-8000 München 40(DE)

(54) **Method for the preparation of ketones.**

(57) Method for the preparation of ketones, by means of oxydation of the corresponding secondary alcohols, characterized in that said alcohols are catalytically oxidized by H_2O_2 inside a two-phase system comprising:

a) an aqueous phase, containing hydrogen peroxide as the oxidizing agent;

b) an organic phase, containing a secondary alcohol and optionally a solvent immiscible with said aqueous phase, as well as a peroxidic catalyst having the general formula $Q_3XW_4O_{24}$, wherein X represents an atom of phosphorus or of arsenic and wherein Q represents a quaternary cation, containing hydrocarbon groups having a total of from 20 to 70 C atoms.

EP 0 232 742 A1

METHOD FOR THE PREPARATION OF KETONES

BACKGROUND OF THE INVENTION

The oxidation of secondary alcohols to ketones is one of the basic reactions of the organic synthesis; as an example, mentioning the oxidation of isoborneol or of borneol for obtaining camphor will be sufficient. Many known processes are based on the oxidation of the corresponding secondary alcohols; such processes show, however, heavy drawbacks. Some (stoichiometrical) processes require the use of considerable amounts of expensive oxidizing agents, or of agents which create heavy environmental problems for their recovery or disposal at the reaction end; as an example, we may mention, besides HNO_3, oxalyl chloride, N-halosuccinimides, and the pentavalent vanadium, hexavalent chromium and heptavalent manganese compounds.

Other (catalytic) processes, although more preferable than the first ones, from the environmental point of view, are not completely satisfactory, because of the long reaction times (see, e.g., the $PdCl_2$/NaOAc/O_2 system, or the benzyltrimethylammonium tetrabromo-oxomolybdate/tert.butyl hydroperoxide system), or because of the particularly expensive (PtO_2 or RuO_4), or toxic (OsO_4) catalysts used. Among the catalytic methods, examples are known of oxidation with hydrogen peroxide, the use of which could offer, in principle, undoubted advantages, thanks to their limited cost and to the absence of a reduction product to be disposed of. But also these methods show a poor practical interest, in that:

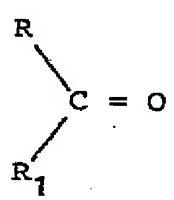
-They require extremely long reaction times (from 1 to 7 days) the catalytic activity being very low (Trost: Israel J. Chem. 1984, 24, 134); or

-It is necessary to work with H_2O_2 at 90%, with evident safety problems (Mares: J. Org. Chem., 1973, 44, 921).

The Applicants have now found that it is possible to oxidize secondary alcohols to ketones by means of a simple and cheap process, free from the drawbacks to be faced in case of the known processes, by using low-concentration aqueous H_2O_2 and resorting to a suitable catalytic system.

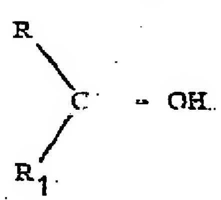
DISCLOSURE OF THE INVENTION

In its broadest aspect, the invention consists of a catalytic method for the preparation of ketones having formula (I):



(I)

by means of oxidation of the corresponding secondary alcohols having formula (II):



(II)

wherein R and R_1, equal to or different from each other, are alkyl or aryl-alkyl groups having up to 20 C atoms, aryl or alkyl-aryl groups having from 6 to 12 C atoms or cycloalkyl groups having from 3 to 12 C atoms; obviously R and R_1 can be bound to each other, so as to form an alkylic cycle containing from 5 to 12 C atoms, or a polycyclic system, containing preferably up to 40 C atoms. The process is characterized

in that said alcohols (II) are oxidized to the corresponding ketones (I) by reacting them with H_2O_2, under stirring at 60-95°C, inside a biphasic system comprising:

a) an aqueous phase, containing hydrogen peroxide as the oxidizing agent;

b) an organic phase, consisting of a secondary alcohol and optionally of a solvent immiscible with said aqueous phase, as well as of a peroxidic catalyst having the general formula $Q_3XW_4O_{24}$ (III), wherein X represents an atom of phosphorus or of arsenic, and wherein Q represents a quaternary cation $(R_2R_3R_4R_5M)^+$, wherein M is selected from nitrogen and phosphorus and wherein R_2, R_3, R_4 and R_5, equal to or different from each other, are selected from hydrogen and hydrocarbon groups, so as to have from 1 to 4 hydrocarbon groups containing a total of from 20 to 70 C atoms.

By such a method, the desired ketones are obtained with optimum yields and in a very pure form; an illustrative, but not limitative example of the alcohols which can be oxidized according to the invention is represented by:

hexane-2-ol;
octane-2-ol;
decane-2-ol;
cyclohexanol;
2,6-dimethyl-cyclohexanol;
menthol;
1-phenyl-ethanol;
borneol;
isoborneol;
6-hydroxy-heptanoic acid;
benzhydrol;
2-ethyl-1,3-hexanediol;
dihydrocholesterol;
1,2,3,4,5,6,7,8-octahydro-2-hydroxy-naphthalene.

Oxidation catalyst (III) is consisting of a peroxidic complex, containing tungsten, phosphorus (or As), and a sufficiently lipophilic quaternary cation, that can be obtained according to usual techniques.

According to a preferred but not limitative form, it is better to use, as a catalyst, a compound having formula (III), wherein X represents phosphorus, wherein M (in the quaternary cation Q) represents nitrogen and wherein R_2, R_3, R_4, R_5 are hy drocarbon groups containing a total of from 25 to 40 C atoms, such as, e.g., methyltrioctylammonium, dimethyldihexadecylammonium, dimethyldioctadecylammonium, or mixtures thereof; in particular, as the catalysts, the compounds having formula:

$$(C_{25}H_{54}N)_3PW_4O_{24} \quad \text{and} \quad (C_{37}H_{78}N)_3PW_4O_{24}$$

$$\text{(IV)} \qquad\qquad\qquad \text{(V)}$$

are preferred.

The catalysts having formula (IV) and (V) can be prepared, e.g., by reacting tungstic acid (or an alkali-metal tungstate), phosphoric acid (or an alkali-metal phosphate) and hydrogen peroxide, inside an acidic aqueous phase, with a quaternary salt, selected from the group consisting of methyltrioctylammonium chloride (known on the market under the trade name ALIQUAT 336) and dimethyl[dioctadecyl (75%) + dihexadecyl (25%)]ammonium chloride (known on the market under the trade name ARQUAD 2HT), contained in an organic phase immiscible with the aqueous phase. The reaction between the inorganic reactants can be carried out at from 20 to 80°C; then the quaternary salt dissolve in a solvent (preferably in 1,2-dichloroethane) is added, preferably at room temperature, and stirring of the biphasic mixture is continued for 15-30 minutes. The acidic aqueous phase has preferably a pH lower than 2; to the purpose of obtaining such a range of values, pH is adjusted, if necessary, with a mineral acid (e.g., H_2SO_4 or HCl). In ge neral, the molar ratios between the reactants must be the following: per each mol of P, 4 mol of W and up to 2 mol of quaternary salt; as to H_2O_2, from 2.5 to 6 mol of H_2O_2 per mol of W are enough. After the separation of the phases, by evaporation of the organic phase, the compound (IV) or the compound (V) is obtained, respectively, in the oil or in the solid form. The oxidation reaction is carried out according to the double-phase technique, and the organic phase contains the alcohol, the catalyst, and, optionally, a solvent immiscible with the aqueous phase; said immiscible solvent can be chlorinated hydrocarbons (e.g., 1,2-dichloroethane, trichloroethanes, tetrachloroethylene) or optionally substituted aromatic hydrocarbons (e. g.,

benzene, toluene or xylenes). Usually, the reaction can be carried out under vigorous stirring, at temperatures from 60° to 95°C and under atmospheric pressure, what does not exclude, obviously, that the reaction may be carried out under a superatmospheric pressure. The reaction time (according to the used catalyst and to its amount, to the operating temperature, to the nature and to the concentration of the alcohol in the organic phase) is generally from 10 minutes to 2 hours; the catalyst is preferably used in a H_2O_2:catalyst molar ratio from 200:1 to 300:1. It is finally recommended to work with an H_2O_2:alcohol molar ratio from 1:1 to 2:1, and preferably from 1.2:1 to 1.5:1. When a suitable solvent is used, the alcohol concen tration in the organic phase is preferably higher than 70% by weight. The concentration of H_2O_2, in the aqueous phase, is not crytical, and can be from 1 to 70%, and preferably from 10 to 40% by weight. At the reaction end, after the separation of the phases, the ketone (present in the organic phase) is isolated by distillation or by column chromatography, according to usual techniques. The method of the invention can be performed by means of usual equipment and techniques; the catalyst is sufficiently stable and can be therefore prepared and stored until its use. The invention is now disclosed in greater detail in the following Examples, given for purely illustrative and non-limitative purposes. The concentration of hydrogen peroxide and of phosphoric acid is expressed in the Examples as grams per 100 cm³ of solution.

EXAMPLE 1

Part A

Preparation of catalyst $(C_{25}H_{54}N)_3PW_4O_{24}$ (IV)

To a 4-neck 100-cm³ flask, equipped with blade stirrer and dropping funnel, 3.30 g of $Na_2WO_4.2H_2O$, dissolved in 20 cm³ of H_2O, 1.5 cm³ of 40% H_3PO_4 and 3 cm³ of H_2SO_4 at 30% by weight were charged at room temperature. Two cm³ of 40% H_2O_2 were then added. Forty cm³ of 1,2-dichloroethane, containing 1.6 g of methyltrioctylammoniumchloride (known in the trade as ALIQUAT 336), were then added, under vigorous stirring, over a 3-minute time. The stirring was maintained for 20 minutes at room temperature, and at the end the reation mixture was decanted and the phases were separated. The organic (lower) phase was evaporated in vacuo, thus obtaining 2.82 g of a viscous oil. The analytical results are in agreement with the indicated formula, as shown hereinbelow:

-Active oxygen found = 5.67% (determined by means of the addition of a known excess of Na_2SO_3 in a basic medium, and iodometric back-titration in acidic medium).

-Theoretical active oxygen = 5.68% (compound for 8 active oxygen atoms).

Part B

Oxidation of 2-octanol

To a 2-neck 50-cm³ flask, provided with magnetic stirrer, termomether and reflux condenser, 6.4 cm³ of 40% H_2O_2 (about 75 mmol), 0.56 g (about 0.25 mmol) of catalyst (IV), and 6.5 g (50 mmol) of 2-octanol were charged. The biphasic mixture was heated under vigorous stirring, at 90°C and was kept at this temperature for 1.5 hours. A conversion of H_2O_2 > 98% was obtained (as determined by iodometric titration of the aqueous phase). At the end, the phases were separated. The aqueous phase was extracted with ethyl ether and the extract was added to the organic phase. The solvent was evaporated off and the residue was eluted over a silica gel column, using an ether/n-hexane (1:1) mixture as the eluent. 5.9 g (46.1 mmol) of 2-octanone were obtained with a purity > 99%, as determined by gas-liquid chromatography (GLC). The yield, with respect to the used alcohol, was 92%.

EXAMPLE 2

Example 1 was repeated, replacing 2-octanol by 1-phenylethanol (6.1 g; 50 mmol), and reducing the reaction time to 10 minutes; 5.4 g (45 mmol) of acetophenone were obtained (GLC purity: 98%),what corresponds to a 90% yield.

EXAMPLE 3

Example 1 was repeated, replacing 2-octanol by (-)-menthol (7.8 g; 50 mmol), increasing the reaction time to 2 hours, and eluting the residue of the organic phase over a column of alumina (instead of silica); 6.78 g (44 mmol) of (-)-menthone were obtained (GLC purity > 99%), what corresponds to a 88% yield.

EXAMPLE 4

Example 1 repeated, replacing 2-octanol by 2-ethyl-1,3-hexanediol (7.3 g; 50 mmol) and reducing the reaction time to 1 hour; 5.48 g (38.1 mmol) of 3-hydroxymethyl-4-heptanone were obtained (GLC purity > 99%), which corresponds to a yield of 76%.

EXAMPLE 5

Example 1 was repeated, replacing 2-octanol by (±)-isoborneol (7.7 g; 50 mmol), adding 2 cm^3 of tetrachloroethylene and reducing the reaction time to 45 minutes. 7.22 g (47.5 mmol) of (±)-camphor were obtained (GLC purity > 99%), what corresponds to a 95% yield.

EXAMPLE 6

Example 3 was repeated, replacing (-)-menthol by 2,6-dimethylcyclohexanol (6.4 g; 50 mmol), using 5.1 cm^3 (60 mmol) of 40% of H_2O_2, adding 4 g of anhydrous $MgSO_4$ and reducing the reaction time to 30 minutes. 5.61 g (44.5 mmol) of 2,6-dimethyl-cyclohexanone were obtained (GLC purity > 99%), what corresponds to a 89% yield.

EXAMPLE 7

Part A

Preparation of catalyst $(C_{37}H_{78}N)_3PW_4O_{24}$ (V)

By operating as described in Example 1, but replacing ALIQUAT 336 with 3.10 g of dimethyl-[dioctadecyl (75%) + dihexadecyl (25%)]ammonium chloride (known in the trade as ARQUAD 2HT), 3.6 g of a white solid were obtained. The analytical values are in agreement with the indicated formula,
-Active oxygen found = 4.60% (determined as in Example 1);
-Theoretical active oxygen = 4.63% (computed for 8 active oxygen atoms).

Part B

Oxidation of benzhydrol

Example 3 was repeated, replacing catalyst (IV) by 0.69 g (0.25 mmol), of catalyst (V), replacing 2-octanol with 9.20 g (50 mmol) of benzhydrol, and reducing the reaction time to 1 hour. 9.04 g (49.7 mmol) of benzophenone were thus obtained (GCL purity > 99%), what corresponds to a 99% yield.

EXAMPLE 8

Example 5 was repeated, replacing (±)-isoborneol by (-)-borneol (7.7 g; 50 mmol); 6.99 g (46 mmol) of (-)-camphor were obtained (GLC purity 97.8%), what corresponds to a 92% yield.

EXAMPLE 9

To a 2-neck 50-cm³ flask, provided with magnetic stirrer, termomether and reflux condenser, 3.2 cm³ of 40% H_2O_2 (37.6 mmol), 10 cm³ of tetrachloroethylene, 0.28 g (about 0.125 mmol) of catalyst (IV), and 9.9 g of 90% dihydrocholesterol (25 mmol) were charged. The biphasic mixture was heated at 90°C under vigorous stirring and was kept at this temperature for 45 minutes. A conversion of H_2O_2 > 98% was obtained (as determined by iodometric titration of the aqueous phase). At the end, the phases were separated. The solvent of the organic phase was evaporated off and the residue was eluted over a silica gel column, using methylene chloride as the eluent. 8.80 g (22.8 mmol) were obtained of cholestan-3-one (melting point: 129-130°C, after crystallization from ethanol). The yield, with respect to the used alcohol, was 91%. Data and results of all of the tests are reported in the following table:

TABLE 1

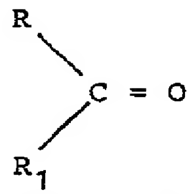
Example	Alcohol (50 mmol) (*)	Catalyst (0.25 mmol)	Solvent	Time	T (°C)	Yield (%)
1	Octanol	IV	-	1.5 hrs	90	92
2	1-Phenylethanol	IV	-	10 min.	90	90
3	(-)-Menthol	IV	-	2.0 hrs	90	88
4	2-Ethyl-1,3-hexanediol	IV	-	1.0 hrs	90	76
5	(±)-Isoborneol	IV	C_2Cl_4	45 min.	90	95
6	Dimethyl-cyclohexanol (**)	IV	-	30 min.	90	89
7	Benzhydrol	V	-	1 hr	90	99
8	(-)-Borneol	IV	C_2Cl_4	45 min.	90	92
9	Dihydrocholesterol	IV	C_2Cl_4	45 min.	90	91

(*) H_2O_2 at 40% (about 75 mmol), but for Example 6;

(**) Addition of anhydrous $MgSO_4$ (4 g); 40% H_2O_2 : 60 mmol.

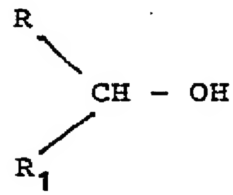
Claims

1. A catalytic method for the preparation of ketones having formula (I):



(I)

by means of oxidation of the corresponding secondary alcohols having formula (II):



(II)

wherein R and R_1, equal to or different from each other, are alkyl or aryl-alkyl groups (having up to 20 C atoms), aryl or alkyl-aryl groups (of from 6 to 12 C atoms) or cycloalkyl groups having from 3 to 12 C atoms; and wherein R and R_1 can be bound to each other, so as to form an alkylic cycle containing from 5 to 12 C atoms, or a polycyclic system, characterized in that said alcohols are oxidized (by reacting them with H_2O_2 under vigorous stirring), preferably at 60-95°C, inside a liquid system comprising:

a) an aqueous phase, containing, as the oxidizing agent, hydrogen peroxide;

b) an organic phase, containing a secondary alcohol and optionally a solvent immiscible with said aqueous phase, as well as a peroxidic catalyst having the general formula $Q_3XW_4O_{24}$ (III), wherein X represents an atom of phosphorus or of arsenic, Q represents a quaternary cation $(R_2R_3R_4R_5M)^+$, M being selected between nitrogen and phosphorus, and wherein R_2, R_3, R_4 and R_5, equal to or different from each other, are selected from hydrogen and hydrocarbon groups, so as to have from1 to 4 hydrocarbon groups containing a total of from 20 to 70 C atoms.

2. A method according to claim 1, wherein the catalyst (III) is selected from the compounds of formula:
$(C_{25}H_{54}N)_3\ PW_4O_{24}$ and
$(C_{37}H_{78}N)_3\ P\ W_4O_{24}$.

3. A method according to claim 1, characterized in that in catalyst (III), X represents phosphorus, that in the quaternary cation M represents nitrogen, and that the radicals R_2, R_3, R_4 and R_5 are hydrocarbon groups containing a total of from 25 to 40 C atoms.

4. A method according to claim 3, wherein the quaternary cation is selected from methyltrioctylammonium, dimethyldioctadecyl ammonium and dimethyl-or dihexadecylammonium or mixtures thereof.

5. A method according to one or more of the claims 1-4, wherein the alcohol is selected from octan-2-ol, 1-phenyl-ethanol, (-)-menthol, 2-ethyl-1,3-hexanediol, (-)-borneol, isoborneol, 2,6-dimethylcyclohexanol, benzhydrol, cyclohexanol, dihydrocholesterol and 1,2,3,4,5,6,7,8-octahydro-2-hydroxy-naphthalene.

6. A method according to one or more of the claims 1-5, wherein the oxidation temperature is from 60 to 95°C, the H_2O_2:alcohol molar ratio being from 1:1 to 2:1 and the H_2O_2:catalyst molar ratio being from 200:1 to 300:1.

7. A method according to one or more of the claims 1-6, wherein the concentration of H_2O_2 in the aqueous phase is from 1 to 70% by weight.

8. A method according to claim 7, wherein said hydrogen peroxide concentration is from 10 to 40% by weight.

9. A method according to one or more of the claims 1-8, wherein the used solvent, immiscible with water, is selected from the chlorinated aliphatic hydrocarbons and the optionally substituted aromatic hydrocarbons.

European Patent Office

EUROPEAN SEARCH REPORT

Application number: EP 87100458.6

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	US - A - 4 259 527 (FRANK MARES et al.) * Claim 1; column 1, line 42 - column 2, line 12 * --	1	C 07 C 45/29 C 07 C 49/00 B 01 J 31/34
A	EP - A2 - 0 102 655 (ANIC) * Claims 1-4 * --	1,6,7	
A	GB - A - 1 530 447 (NATIONAL RESEARCH) * Page 1 * ----	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)
C 07 C 45/00 C 07 C 49/00 B 01 J

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	20-03-1987	REIF

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document
T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons
& : member of the same patent family, corresponding document

EPO Form 1503 03 82